

Cardiovascular Effects of Caffeine

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SUMMARY

A review of the literature on the cardiovascular effects of caffeine indicates that moderate caffeine consumption does not cause cardiac arrhythmias, hypertension, or an increased incidence of coronary heart disease. Caffeine use is often associated with atherogenic behavior, such as cigarette smoking. Failure to take into account covariables for cardiovascular disease could be responsible for commonly held misconceptions about caffeine and heart disease.

RÉSUMÉ

Une revue de la littérature portant sur les effets cardiovasculaires de la caféine indique que la consommation modérée de café ne provoque pas d'arythmie cardiaque, d'hypertension ou d'augmentation de l'incidence de la coronaropathie. La consommation de café s'accompagne souvent d'un comportement athérogénique tel le tabagisme de la cigarette. Il se pourrait que le fait de ne pas tenir compte des covariables impliquées dans la maladie cardiovasculaire soit responsable des conceptions erronées entendues fréquemment autour de la caféine et des cardiopathies.

Can Fam Physician 1992;38:1459-1462.

DOES CAFFEINE CAUSE CARDIAC arrhythmias? Does caffeine increase heart rate? Does caffeine increase blood pressure? Does caffeine cause coronary heart disease (CHD)?

The effects of caffeine on the heart and circulation have been scrutinized by scientists for well over 50 years. Despite extensive research, the precise cardiovascular effects of caffeine continue to be debated. For example, two recent studies^{1,2} involving 10 000 and 45 000 subjects reached opposite conclusions about a possible association between coffee intake and the development of CHD. In this review, the above questions will be answered based upon the currently available scientific evidence.

Confounding variables

One of the greatest difficulties in determining the effects of long-term coffee use in humans is the potential influence of confounding variables. The best example is cigarette smoking. Repeated observations in clinical studies^{1,3,4} have demonstrated a clear link between a higher consumption of coffee and smoking. Coffee drinkers tend to consume more alcohol, have a higher blood glucose level, be more obese, and in-
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gest more cholesterol-containing foods.¹ The same is not true for tea drinkers, who are generally people with healthier lifestyle characteristics.¹

Because much of the research on caffeine has involved population studies, one must account for possible confounding variables. However, adjustments in the data analysis are often difficult to achieve. For instance, if participants in a study examining a possible link between coffee and CHD underestimate their cigarette smoking, then part of any increase in CHD would be attributed to coffee use and not smoking. Similarly, if subjects with higher coffee intake have stopped smoking in the past few years (as many have) or smoke intermittently, grouping these individuals with nonsmokers makes their higher coffee use appear to be the cause of an increased incidence of CHD.

Coffee and arrhythmias

A recent review⁵ has examined all major clinical studies on the possible association between coffee consumption and cardiac arrhythmias.

In five placebo-controlled trials,⁶⁻¹⁰ in normal subjects and patients with cardiovascular disease, doses of caffeine up to 500 mg daily (equivalent to four to six cups of coffee) did not increase the frequency or severity of cardiac arrhythmias, including premature ventricular complexes, ventricular couplets, or ventricular tachycardia.

Indeed, Graboyes et al¹⁰ administered caffeine (200 mg) or placebo to patients with known malignant ventricular arrhythmias. A 3-hour period of Holter electrocardiographic monitoring showed no increase in the frequency or severity of arrhythmias after caffeine use compared with the results after placebo administration, despite the occurrence of ventricular tachycardia on both study days.

In a more recent report, Chelsky et al¹¹ performed electrophysiologic testing with and without caffeine (275 mg) in 22 patients with a history of symptomatic, non-sustained ventricular tachycardia. The authors found no evidence of any caffeine-induced alterations in the induction or severity of ventricular arrhythmias.

In an electrophysiologic study¹² involving seven healthy volunteers and 12 patients with heart disease, the administration of caffeine was found to have no appreciable effect on cardiac conduction. However, in several highly selected subjects with a previous diagnosis of "caffeine sensitivity," caffeine could have aggravated a pre-existing predilection to arrhythmogenesis. Whether these findings can be generalized to the average cardiac patient, including those with known arrhythmias, is difficult to assess.

One epidemiologic study¹³ has examined premature ventricular complex occurrence in 7311 people who had a 2-minute single-lead electrocardiogram recording. Multivariate analysis suggested that only a very high coffee intake of nine or more cups daily was associated with a doubling of the likelihood of at least one premature ventricular complex appearing on the rhythm strip. As noted above, interpretation of these findings is made difficult by the likelihood that other factors, such as concurrent cigarette smoking, contributed to the development of arrhythmias in this rather select group of very heavy coffee users.

Overall, the available clinical data indicate that moderate caffeine consumption does not increase the frequency or severity of cardiac arrhythmias in normally healthy persons, in patients with ischemic heart disease, or even in patients with pre-existing serious ventricular ectopy.

Caffeine and heart rate

When giving lectures to groups of physi-

cians, I have frequently encountered a general opinion that coffee is a stimulant, causing an increase in heart rate. Indeed, in our own initial research studies,^{10,11} we were perplexed to find that caffeine not only failed to increase heart rate but actually seemed to reduce it slightly. However, other studies have now shown similar results, including a recent report¹⁴ on ambulatory blood pressure monitoring in which we detected a small, but statistically significant, decline in heart rate following caffeine ingestion compared with placebo during the first day of caffeine use in 25 healthy subjects who had not previously been caffeine users.

As often happens in science, what at first appears to be an original observation – that caffeine decreases and not increases heart rate – turns out simply to replicate earlier findings. Although not quoted in recent publications, a 1968 report¹⁵ also noted a bradycardic effect of caffeine. Of interest was the slower heart rate that occurred only in caffeine-naïve subjects; results identical to our own recent "original" findings.

Caffeine and blood pressure

Numerous studies¹⁶ have shown that 200 to 300 mg of caffeine will cause a modest increase in blood pressure of about 8 to 12 mm Hg systolic and 5 to 7 mm Hg diastolic, but only if administered to subjects who have not recently consumed caffeine-containing beverages or foods. When these same subjects are given caffeine on a regular basis, the blood pressure returns to baseline values within 2 to 3 days, presumably because of development of tolerance.

Large epidemiologic studies have also examined the possible association between coffee and tea use and blood pressure. Several reports¹⁶ have found a small increase in systolic or diastolic blood pressure, but other studies have reported opposite findings, with increasing coffee intake associated with a lower blood pressure reading.

Using a novel pharmaco-epidemiologic approach, Sharp and Benowitz¹⁷ found that healthy persons who consumed caffeine intermittently had a slightly higher blood pressure than regular users, once again suggesting that a tolerance develops to caffeine's effects on blood pressure. In a recent study¹⁴ using ambulatory blood

pressure monitoring, caffeine (400 mg) increased ambulatory daytime blood pressure by 3/3 mm Hg in 25 caffeine-naïve subjects. The ambulatory blood pressure returned to baseline by the third day of chronic caffeine ingestion.

Thus, regular ingestion of caffeine does not appear to increase blood pressure. However, infrequent use can cause a small, clinically unimportant increase in blood pressure when persons consuming caffeine have not developed tolerance to its effects.

Caffeine and CHD

Recent Canadian nutrition guidelines¹⁸ have recommended that people not consume more than four cups of coffee daily, solely on the basis of a possible association between coffee and CHD. What evidence exists to support this conclusion? Eleven longitudinal cohort studies^{2,4,19-27} have reported on coffee as a possible contributor to the development of CHD. Eight of these reports, including the Framingham Heart Study,²⁵ did not find any evidence to link increased coffee use with CHD. Three studies showed a positive association. A Norwegian study²⁷ reported that a daily intake of nine or more cups of coffee was related to an increased risk of experiencing CHD. However, the preparation of coffee in Norway is different from that in North America in that coffee in Norway is usually boiled, a process that appears to have other effects, such as causing an increase in serum cholesterol.²⁸ Brewing methods in North America have not been shown to increase cholesterol.

Another study²³ from the United States found no increase in CHD in people who drank four to five cups of coffee daily but did report an increased risk of CHD in individuals consuming six or more cups of coffee daily. The only study that appears to substantiate the Canadian nutrition guidelines is a report⁴ that more than four cups daily is associated with an increased risk of cardiovascular events. However, this was a comparatively small study with only nine end points occurring in the more than four cups daily category.

Thus, the evidence in support of the recent Canadian nutrition guidelines¹⁸ appears to be based on only one study with nine end points. Otherwise, considerable

data seem to disprove any association between coffee use and CHD, at least for those consuming up to 6 cups daily. Moreover, very heavy consumers of coffee can have potentially confounding lifestyle traits, such as cigarette smoking,²⁹ and so it would seem premature to promote strict guidelines on coffee intake until further data are available.

Conclusion

From a cardiovascular viewpoint, caffeine appears to be a target for unproved beliefs that its use is associated with the development of cardiac arrhythmias, an increase in heart rate, higher blood pressure, and a higher incidence of CHD. Despite extensive clinical research, little evidence exists to support caffeine as a significant contributor to any cardiovascular disease.

The authors of the recent Canadian nutrition guidelines¹⁸ agree that there is no association between caffeine and cardiac rhythm disturbances or hypertension, but appear to have been influenced by a single, albeit widely reported, article (involving comparatively few cardiovascular end points), which found an association between coffee use and CHD.⁴ Even the principal author of that article has stated in a recently published correspondence³⁰ that "we have no definitive answer to the question of whether coffee increases the risk of CHD" and "the totality of the evidence remains equivocal." This view is consistent with the available data and suggests that further research is required before coffee is listed as a cause of CHD. ■

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References

1. Klatsky AL, Friedman GD, Armstrong MA. Coffee use prior to myocardial infarction restudied: heavier intake may increase the risk. *Am J Epidemiol* 1990;132:479-88.
2. Grobbee DE, Rimm EB, Giovannucci E, Colditz G, Stampfer M, Willett W. Coffee, caffeine and cardiovascular disease in men. *N Engl J Med* 1990;323:1026-32.
3. Greenland S. Quantitative methods in the review of epidemiologic literature. *Epidemiol Rev* 1987;9:1-30.
4. La Croix AZ, Mead LA, Kung-Yee L, Bedell C, Pearson TA. Coffee consumption and the incidence

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Occlusive therapy contraindicated in patients with atopic dermatitis. **Precautions:** Because of the potential hazard of nephrotoxicity and ototoxicity, avoid prolonged use or use of large amounts in the treatment of skin infections following burns, trophic ulceration and other conditions where absorption of neomycin is possible. As with any antibiotic preparation, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi other than *Candida*. Constant observation of the patient is essential. Should superinfection due to nonsusceptible organisms occur, Kenacomb should be discontinued and appropriate therapy instituted. Although adrenal suppression and other systemic adverse effects are rare with topical corticosteroid preparations, their possible occurrence must be kept in mind, particularly when these preparations are used over large areas or for an extended period of time. 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Delayed healing and systemic effects, including adrenal suppression and subcapsular cataracts, may occur if absorbed in appreciable amounts. **Dosage:** Cream: rub into affected areas 2 to 3 times daily. Ointment: Apply a thin film to the affected areas 2 to 3 times daily. Mild Cream & Ointment: 3 or 4 times daily. **Supplied: Cream and Ointment:** Each g contains: triamcinolone acetonide 1 mg, neomycin base (as sulfate) 2.5 mg, gramicidin 250 µg, nystatin 100 000 units. The cream is formulated in a perfumed aqueous vanishing cream base which permits its use even in moist intertriginous areas. It also contains polysorbate 60, alcohol, aluminum hydroxide concentrated wet gel, titanium dioxide, silicone fluid, propylene glycol, ethylenediamine, hydrochloric acid, white petroleum, polyoxyethylene fatty alcohol ether, methyl and propyl parabens and sorbitol solution. Tubes of 15, 30 and 60 g. 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of coronary heart disease. *N Engl J Med* 1986;315:977-82.

5. Myers MG. Caffeine and cardiac arrhythmias. *Ann Intern Med* 1991;114:147-50.
6. Sutherland DJ, McPherson DD, Renton KW, Spencer CA, Montague TJ. The effect of caffeine on cardiac rate, rhythm and ventricular repolarization. *Chest* 1985;87:319-24.
7. Newcombe PF, Renton KW, Rautaharju PM, Spencer CA, Montague TJ. High-dose caffeine and cardiac rate and rhythm in normal subjects. *Chest* 1988; 94:90-4.
8. Myers MG, Harris L, Leenen FH, Grant DM. Caffeine as a possible cause of ventricular arrhythmias during the healing phase of acute myocardial infarction. *Am J Cardiol* 1987;59:1024-8.
9. Myers MG, Harris L. Caffeine and ventricular arrhythmias. *Can J Cardiol* 1990; 6:95-8.
10. Graboyes TB, Blatt CM, Lown L. The effect of caffeine on ventricular ectopic activity in patients with malignant ventricular arrhythmia. *Arch Intern Med* 1989; 149:637-9.
11. Chelsky LB, Cutler JE, Griffith K, Kron J, McClelland JH, McAnulty JH. Caffeine and ventricular arrhythmias. *JAMA* 1990;264:2236-40.
12. Dobmeyer DJ, Stine RA, Leier CV, Greenberg R, Schaal SF. The arrhythmogenic effects of caffeine in human beings. *N Engl J Med* 1983;308:814-6.
13. Prineas RJ, Jacobs DR, Crow RS, Blackburn H. Coffee, tea and VPB. *J Chronic Dis* 1980;33:67-72.
14. Myers MG, Reeves RA. The effect of caffeine on daytime ambulatory blood pressure. *Am J Hypertens*. 1991;4:427-31.
15. Colton T, Gosselin RE, Smith RP. The tolerance of coffee drinkers to caffeine. *Clin Pharmacol Ther* 1968;9:31-9.
16. Myers MG. Effects of caffeine on blood pressure. *Arch Intern Med* 1988;148: 1189-93.
17. Sharp DS, Benowitz NL. Pharmacoepidemiology of the effect of caffeine on blood pressure. *Clin Pharmacol Ther* 1990; 47:57-60.
18. Scientific Review Committee. *Nutrition recommendations*. Report of The Scientific Review Committee. Ottawa, Ont: Health and Welfare Canada, 1990:194.
19. Yano K, Rhoads GG, Kagan A. Coffee, alcohol and risk of coronary heart disease among Japanese men living in Hawaii. *N Engl J Med* 1977;297:405-9.
20. Wilhelmsen L, Tibblin G, Elmfeld ED, Wedel H, Werko L. Coffee consumption and coronary heart disease in middle-aged Swedish men. *Arch Intern Med* 1978;138:1472-5.
21. Murray SS, Bjelke E, Gibson RW, Schuman LM. Coffee consumption and mortality from ischemic heart disease and other causes: results from the Lutheran Brotherhood Study, 1966-1978. *Am J Epidemiol* 1981;113:661-7.
22. Jacobsen BK, Bjelke E, Kvale G, Heuch I. Coffee drinking, mortality and cancer incidence: results from a prospective Norwegian study. *J Natl Cancer Inst* 1986;76:823-31.
23. Le Grady D, Dyer AR, Shekelle RB, Stamler J, Liu K, Paul O, et al. Coffee consumption and mortality in the Chicago Western Electric Company Study. *Am J Epidemiol* 1987;126:803-12.
24. Martin JB, Annegers JF, Curb JD, Heyden S, Howson C, Lee ES, et al. Mortality among hypertensives by reported level of caffeine consumption. *Prev Med* 1988;17:310-20.
25. Wilson PWF, Garrison RJ, Kannel WB, McGee DL, Castelli WP. Is coffee consumption a contributor to cardiovascular disease? *Arch Intern Med* 1989; 149:1169-72.
26. Tverdal A, Stensvold I, Solvoll K, Foss OP, Lund-Larsen P, Bjartveit K. Coffee consumption and death from coronary heart disease in middle aged Norwegian men and women. *Br Med J* 1990; 300:566-9.
27. Rosengren A, Wilhelmsen L. Coffee, coronary heart disease and mortality in middle-age Swedish men; findings from the Primary Prevention study. *J Intern Med* 1991;230:67-71.
28. Stensvold I, Tverdal A, Foss OP. The effect of coffee on blood lipids and blood pressure. *J Clin Epidemiol* 1989;42:877-84.
29. Puccio EM, McPhillips JB, Barrett-Connor E, Ganiats TG. Clustering of atherogenic behaviors in coffee drinkers. *Am J Public Health* 1990;80:1310-3.
30. La Croix AZ. Coffee, caffeine and cardiovascular disease. *N Engl J Med* 1991; 324:991-2.

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